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PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 72 (2018), No. 6 (717), pp. 307–312.
DOI: 10.2478/prolas-2018-0044

LACK OF ASSOCIATION BETWEEN RS2067474 POLYMORPHISM IN THE HISTAMINE RECEPTOR H2 GENE AND GASTRIC CANCER IN LATVIAN POPULATION

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Histamine has an important role in the process of the gastric mucosa inflammation acting via histamine receptor H2 (encoded by the gene HRH2*). Single nucleotide polymorphism of the enhancer element of* HRH2 *gene promoter rs2067474 (1018 G > A) may be associated with changes of expression of the receptor. We attempted to clarify the association of this polymorphism with gastric cancer and/or atrophic gastritis in the Latvian (Caucasian) population. The study group consisted of 121 gastric cancer patients and 650 patients with no evidence of gastric neoplasia on upper gastrointestinal endoscopy. Genotyping for rs2067474 was performed with the TaqMan probe-based system using a commercially available probe for RT-PCR. The frequency of the A allele in the gastric cancer group was 0.41% and in the control group — 1.54% (*p *= 0.231). No significant differences were found comparing genotypes between gastric cancer versus control patients (OR = 0.236, CI95% = 0.030–1.896), patients with (n = 165) versus without (n = 485) gastric metaplastic lesions (OR = 0.854, CI95% = 0.288–2.540) and patients with (n = 297) and without (n = 353) gastric atrophic lesions (OR = 1.145, CI95% = 0.451–2.906). Our findings suggest that the* HRH2 *-1018 G > A polymorphism (rs2067474) is neither associated with gastric cancer nor the grade of atrophic gastritis in the Latvian (Caucasian) population.*

Key words: *histamine H2 receptor, gastric cancer, chronic gastritis, genetic polymorphism.*

INTRODUCTION

Gastric cancer still remains the third cause of cancer death in both genders and the fifth most incident cancer worldwide (Ferlay *et al*., 2012). The World Health Organisation (WHO) International Agency for Research on Cancer (IARC) has recognised *Helicobacter pylori* (*H. pylori*) as a Group-one carcinogen for gastric cancer development since 1994 (Anonymous, 1994). Nevertheless, only over 1–2% of patients infected with *H. pylori* will develop gastric cancer

* All authors met the criteria for authorship as estimated by the International Committee of Medical Journal Editors and were involved in the study design preparation, sample collection and patient recruitment, data analysis, analysis of the literature and paper preparation.

during their lifetime (Parsonnet *et al*., 1991). Gastric cancer pathogenesis is a complex process involving both host and bacterial genetic factors, which play a role in the development of the inflammation, epithelial transformation, etc. (Wroblewski *et al*., 2010; Alzahrani *et al*., 2014). Many recent studies have focused on the role of single nucleotide polymorphisms (SNP) involved in the gastric carcinogenesis (Wroblewski *et al*., 2010), which are selected either from genome-wide association studies or because the gene-encoded product is or may be involved in gastric cancer pathogenesis.

The gastrointestinal tract is rich in neuroendocrine cells producing various hormones: G cells produce gastrin, D cells produce somatostatin, enterochromaffin-like (ECL) cells produce histamine and others (Ched *et al*., 2006). Histamine-producing ECL cells are located in the oxyntic mucosa of the stomach and have paracrine appearance (Hananson *et al*., 1986). Histamine has various biological effects acting via four types of histamine receptors (Hill *et al*., 1997; de Ersh *et al*., 2005); stimulation of histamine H2 receptor (HRH2) plays a crucial role in the regulation of gastric acid secretion (Hill *et al*., 1997; Ched *et al*., 2006). Histamine has an important role in the process of the gastric mucosa inflammation acting via HRH2, albeit *H. pylori* infection is the major contributing factor in the development of inflammation (McGowan *et al*., 1996).

The HRH2-encoding gene is located on the 5q35.2 chromosome. SNP of the enhancer element of the *HRH2* gene promoter rs2067474 results in the transition of –1018 G > A and may be associated with changes of expression of the receptor (Guo *et al*., 2005). Currently, only few papers on the association of *HRH2* SNP rs2067474 with gastric mucosa atrophy and gastric cancer have been published, in the Japanese population by Arisawa's group (Arisawa *et al*., 2012; Yamada *et al*., 2012).

The aim of our study was to determine if there is an association of *HRH2* –1018 G > A (rs2067474) genotype with gastric cancer and/or atrophic gastritis in the Latvian (Caucasian) population, which has European ancestry.

MATERIALS AND METHODS

Study design. Gastric cancer patients (n = 121) from Rīga East Clinical University Hospital (Latvia) with an established diagnosis were invited to participate in the study.

Patients (n = 650) being referred for upper gastrointestinal endoscopy to the outpatient department of Rīga East Clinical University Hospital or Centre of Digestive Diseases "GASTRO" (Latvia) due to dyspeptic symptoms were included in the control group. The following exclusion criteria were used: gastric lymphoma, gastric dysplasia, cancer of the oesophagus, Barrett's oesophagus and history of previous gastric surgery. All patients who participated in the study were Caucasians. All patients were invited to participate in the study during the time period 2010–2014.

A blood sample with EDTA anticoagulant was taken from each patient for DNA extraction with further genotyping. DNA was extracted from whole blood using the phenol-chlorophorm method. All control group patients underwent upper gastrointestinal tract endoscopy with further histopathological evaluation of the biopsies.

Upper gastrointestinal tract endoscopy. The upper gastrointestinal tract endoscopy was performed after night-time fasting. Standard biopsy material from each patient was taken during the procedure from at least five different locations in the stomach: two from corpus mucosa (one from the lesser and one from the greater curvature), one from incisura angularis mucosa (from the lesser curvature) and two from antral mucosa (one from the lesser and one from the greater curvature) (Dixon *et al*., 1996). Additional biopsies were taken from any columnar-lined mucosa in the oesophagus and sites suspicious for neoplastic lesions in the stomach and oesophagus.

Histopathology. Three experienced expert gastrointestinal pathologists, blinded to any clinical data, separately examined all the biopsies for controls. All histopathological findings were reported separately for each biopsy site from the stomach: corpus mucosa, incisura angularis mucosa and antrum mucosa. The slides were stained with hematoxylin-eosin, Alcian blue and Giemsa. Metaplastic epithelial changes, *H. pylori* colonisation and gastric mucosa atrophy were scored using visual analogue scales (0 = absents, 1 = mild, 2 = moderate, 3 = severe), according to the updated Sydney classification system (Dixon *et al*., 1996). All results were transformed into the OLGIM and OLGA staging systems (Rugge *et al*., 2013).

In case the difference in the evaluation scores of any position by at least of two points was considered significant, all such cases were reassessed by all three pathologists together until consensus agreement was reached.

All histopathological slides from gastric cancer surgery cases were reassessed by two expert gastrointestinal pathologists. The slides were stained with hematoxylin-eosin. Consensus agreement about each case was achieved. Whenever proper morphological material was available (in accordance to WHO standards) (Bosman *et al*., 2010), subtyping according to the Lauren classification was done (Lauren, 1965).

Genotyping of polymorphisms. DNA was extracted by the standard phenol-chloroform method. Genotyping for rs2067474 (–1018 G > A) was performed with the TaqMan Probe-based system (Applied Biosystems Inc., Carlsbad, CA, USA) using a commercially available probe (C_15859301_10) on an automatic sequence detection instrument (Real-Time PCR System, Applied Biosystems Inc., Carlsbad, CA, USA). Reactions were carried out under the standard conditions as recommended by the manufacturer.

Serology. Blood samples for serological evaluation were taken prior to surgery (in gastric cancer patients) and prior

to upper gastrointestinal endoscopy (in controls). Blood serum was separated from the whole blood and stored frozen at –80 °C in the laboratory. All serum samples were analysed using an enzyme-linked immunosorbent assay kit for *H. pylori* detection (Helicobacter pylori EIA Test kit, GastroPanel®, Biohit Oyj., Helsinki, Finland). Reactions were carried out under the standard conditions as recommended by the manufacturer. Patients were considered seropositive if the anti-*H. pylori* level was equal or higher than 30 EIU/mL.

Statistical analysis. Age was expressed as median and interquartile range (IQR), the comparison between groups was done using the Median test for independent samples. Ratio of gender, *H. pylori* serology, *H. pylori* histology, *HRH2* gene alleles and genotypes were compared using the Fisher's exact test. Adjusted odds ratio (OR) and 95% confidence interval (CI95%) were calculated using logistic regression analysis. Allele and genotype frequencies were calculated by direct count. The relationship of age with OLGIM and OLGA stage in different genotypes was assessed with the Spearman's rank correlation coefficient (r2). All analyses and charts were made using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) and post hoc statistical power estimation was done using the OSSE online calculator (http://osse.bii.a-star.edu.sg/calculation2.php).

Ethical considerations. The Central Medical Ethics Committee of Latvia (No A-11 (15.12.2010)) approved the study protocol before patient recruitment was started. All the patients signed informed consent forms before the enrolment according to the Helsinki declaration.

RESULTS

The characteristics of both study groups are shown in Table 1. Male/female ratio, mean age, and positive *H. pylori* serology ratio were significantly higher in the gastric cancer patients. The AA genotype was not present in the gastric cancer group nor among the control group members. In the control group, the AG genotype was found in 20 patients and GG — in 630. It was in the Hardy-Weinberg equilibrium (p 0.05). The frequency of the A allele in the gastric cancer group was 0.41% and in the control group — 1.54%. There was no significant difference comparing genotype ratios between both study groups (p = 0.228). After adjusting for gender, age and *H. pylori* serology, no significant difference in genotype frequency was identified (OR = 0.236, CI95% = 0.030–1.896, p = 0.176).

According to the Lauren classification, 61/121 patients had intestinal type gastric cancer, 34/121 — diffuse, 18/121 — mixed-type and 8/121 — indeterminate. In accordance to the TNM classification, 25/121 patients had stage I disease, 37/121 — stage II disease, 52/121 — stage III disease, 4/121 — stage IV disease and for three patients, no data was available (Edge *et al*., 2009). The only patient with the AG genotype in the cancer group had mixed-type gastric cancer and stage III disease.

Table 1

CHARACTERISTICS OF STUDY GROUPS AND GENOTYPE FREQUENCIES (–1018 G > A)

	Gastric cancer group	Control group	*p*
Number of subjects	121	650	
Gender			
male	73 (60.3%)	195 (30.0%)	< 0.001[a]
female	48 (39.7%)	455 (70.0%)	
Median of age (IQR), years	65.0 (56.5-73.5)	49.0 (35.0-63.0)	< 0.001[b]
H. pylori serology			
positive	91 (75.2%)	367 (54.5%)	< 0.001[c]
negative	30 (24.8%)	282 (45.5%)	
on genotype			
AA	0	0	0.228[d]
AG	1	20	
GG	120	630	
A allele frequency	0.41%	1.54%	0.231[e]

IQR, interquartile range; [a] ratio of gender between groups; [b] medians of age between groups; [c] ratio of *H. pylori* serology between groups; [d] ratio of AG and GG genotypes between groups; [e] ratio of A allele frequency between groups

The control group was subdivided into two groups according to the OLGIM classification system: one group having an OLGIM 0 stage (n = 485) and the other group having an OLGIM I-IV stage (n = 165). The general characteristics of those groups are shown in the Table 2. After adjusting for

Table 2

CHARACTERISTICS OF THE CONTROL GROUP AND GENOTYPE FREQUENCIES IN ACCORDANCE TO THE OLGIM CLASSIFICATION

	OLGIM I–IV	OLGIM 0	*p*
Number of subjects	165	485	
Gender			
male	54 (32.7%)	141 (29.1%)	0.378[a]
female	111 (67.3%)	344 (70.9%)	
Median of age (IQR), years	59.0 (49.0-70.0)	44.0 (32.5-59.0)	< 0.001[b]
H. pylori serology			
positive	62 (37.6%)	220 (45.5%)	0.084[c]
negative	103 (63.4%)	265 (54.5%)	
H. pylori histology			
positive	96 (58.2%)	230 (47.4%)	0.019[d]
negative	69 (41.8%)	255 (52.6%)	
HRH2 genotype			
AA	0	0	1.000[e]
AG	5	15	
GG	160	470	
A allele frequency	1.51%	1.55%	1.000[f]

IQR, interquartile range; [a] ratio of gender between groups; [b] medians of age between groups; [c] ratio of *H. pylori* serology between groups; [d] ratio of *H. pylori* histology between groups; [e] ratio of AG and GG genotypes between groups; [f] ratio of A allele frequency between groups

Table 3

CHARACTERISTICS OF THE CONTROL GROUP AND GENOTYPE FREQUENCIES IN ACCORDANCE TO THE OLGA STAGE CLASSIFICATION

	OLGA I–IV	OLGA 0	*p*
Number of subjects	297	353	
Gender			
male	78 (26.3%)	117 (33.1%)	0.059[a]
female	219 (73.7%)	236 (66.9%)	
Median of age (IQR), years	59.0 (45.0-69.0)	43.0 (32.0-58.0)	< 0.001[b]
H. pylori serology			
positive	104 (35.0%)	178 (50.6%)	< 0.001[c]
negative	193 (65.0%)	174 (49.4%)	
H. pylori histology			
positive	173 (58.2%)	153 (43.3%)	< 0.001[d]
negative	124 (41.8%)	200 (56.7%)	
HRH2 genotype			
AA	0	0	0.821[e]
AG	10	10	
GG	287	343	
A allele frequency	1.68%	1.42%	0.822[f]

IQR, interquartile range; [a] ratio of gender between groups; [b] medians of age between groups; [c] ratio of *H. pylori* serology between groups; [d] ratio of *H. pylori* histology between groups; [e] ratio of AG and GG genotypes between groups; [f] ratio of A allele frequency between groups

age and *H. pylori* histology, no significant difference was identified in the genotypes (OR = 0.854, CI95% = 0.288–2.540, $p = 0.778$). Both groups had similar A allele frequencies of 1.51% and 1.55%, respectively OLGIM I-IV and OLGIM 0. All patients with the AG genotype in the OLGIM I–IV subgroup had the OLGIM I stage. There were 110 patients with OLGIM stage I, 32 — with stage II, 13 — with stage III and five — with stage IV.

In addition, the control group was subdivided into two groups according to the OLGA stage classification system: one group having the OLGA stage 0 (n = 353) and the other group having the OLGA stage I–IV (n = 297). The general characteristics of those groups are shown in Table 3. After adjusting for age, *H. pylori* serology and *H. pylori* histology, no significant difference was identified in the genotypes (OR = 1.145, CI95% = 0.451–2.906, $p = 0.776$). Both groups had similar A allele frequencies of 1.42% and 1.68%, respectively, OLGA stage I–IV and OLGA stage 0. All patients (n = 10) with the AG genotype in the OLGA stage I–IV subgroup had the OLGA stage I. There were 233 patients with OLGA stage I, 41 — with stage II, 17 — with stage III and six — with stage IV.

In the control group patients with the GG genotype had an increase of both OLGIM and OLGA stage with age (see Figure 1 and Figure 2, respectively), respectively r2 = 0.332 ($p < 0.001$) and r2 = 0.299 ($p < 0.001$). No significant difference was found in patients with the AG genotype.

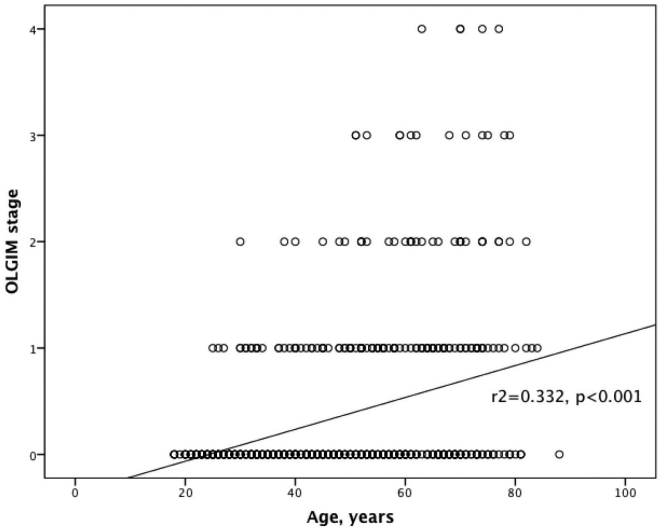

Fig. 1. Relationship of OLGIM stage and age in patients with the GG genotype.

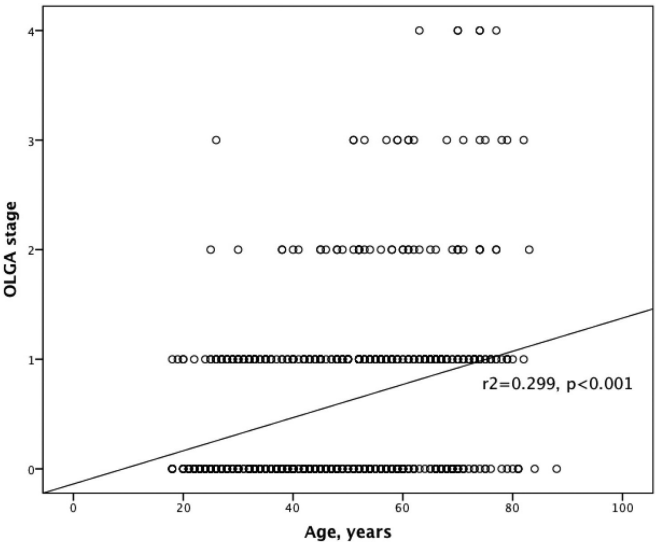

Fig. 2. Relationship of OLGA stage and age in patients with the GG genotype.

Post hoc statistical power estimation (desired significance level 0.05) was done. Statistical power of A allele frequency and gastric cancer was 21.1%.

DISCUSSION

Several reports on the role of *HRH2* –1018 G > A (rs2067474) polymorphism in the risk of human disease development are currently available. Many reports are focused on the association of *HRH2* –1018 G > A polymorphism and diseases of the central nervous system (Mancama *et al*., 2002; Garcia-Martin *et al*., 2008) and breast cancer (Cai *et al*., 2015). However, only a few studies have addressed the potential associations to gastric precancerous lesions, i.e. atrophic gastritis (Arisawa *et al*., 2012; Yamada *et al*., 2012), and the only study addressing the association to gastric cancer was the one by Arisawa *et al*. (2012).

In our study, we were unable to identify any significant differences in the distribution of *HRH2* –1018 G > A genotype among gastric cancer patients in comparison to patients with no gastric cancer. There was also no difference observed when comparing patients with intact gastric mucosa to patients with atrophic gastritis. In the study of Arisawa there was a significant association of gastric cancer and *HRH2* –1018 G > A polymorphism, and A allele presence was considered as a protective factor for gastric cancer (Arisawa *et al*., 2012). The positive result of the study partially may be explained by the higher frequency of the A allele in the Japanese population.

The *HRH2* –1018 A allele frequency in Latvian non-gastric cancer patient group was 1.54% only. That is lower than in the patient sample from Arisawa's study (13.5%) (Arisawa *et al*., 2012) and also lower than in healthy Spanish population (5.0%) (Garcia-Martin *et al*., 2008). There are known differences among populations in the A allele frequency, e.g., the 1000 Genomes Project data showed a general frequency in European populations of 4% (ranging from 3.3% in the Iberian population of Spain to 5.6% in Finland) and in Eastern Asians — 13.9% (from 9.6% in Japanese from Tokyo to 17% in Han Chinese in Beijing, China) (www.1000genomes.org) (Auton *et al*., 2015).

The main limitation of the study was the small statistical power on the post hoc analysis due to a very small frequency of the A allele in the Latvian population. Some other limitations of the study were male/female ratio; mean age and positive *H. pylori* serology ratio were significantly higher in the gastric cancer patients. For this reason, adjustment for these factors was done, but still no significant difference among genotype distribution was identified. Another limitation was that the control group patients were represented by the population of patients with various symptoms from the upper digestive tract.

In our study, we did not observe any association of *HRH2* –1018 G > A polymorphism with different OLGIM and OLGA stages. The A allele frequency was similar in patients with intact gastric mucosa compared to patients with changes of various degrees in gastric mucosa. However, we could identify only a weak correlation of age with OLGA and OLGIM score in non-gastric cancer patients with GG genotype. Even so, one Japanese group published several reports, where a significant association of GG genotype with metaplasia and/or atrophy of gastric mucosa was found in persons older than 60 years (Arisawa *et al*., 2012; Yamada *et al*., 2012).

Many publications (Lampiasi *et al*., 2007; Gricco *et al*., 2008) are available regarding the role of histamine in the development of gastrointestinal cancers. The SNP of the enhancer element of the *HRH2* gene promoter rs2067474 may be associated with changes of expression of the receptor and/or function of HRH2. In experimental models with gastric cancer cell lines, it was found that stimulation of HRH2 stimulates an increase of cAMP production (Ermani *et al*., 1983), which in advance stimulates the growth of gastric cancer (Kong *et al*., 2012). It was also found that the rs2067474 GG homozygote is associated with CDH1 and DAPK methylation, which is crucial for gastric carcinogenesis (Nomura *et al*., 2013). Even so, the current data available do not identify the precise role of *HRH2* –1018 G > A (rs2067474) polymorphism in the gastric carcinogenesis.

In conclusion, our findings suggest that the *HRH2* –1018 G > A polymorphism (rs2067474) is neither associated with gastric cancer nor the grade of atrophic gastritis in the Latvian (Caucasian) population. The frequency of the A allele in the Latvian (Caucasian) population is extremely different from the Japanese population and is the lowest among European populations. Future epidemiological studies are needed based on a larger sample size in populations with very low A allele frequency, such as the Latvian population, including at least 1500 patients in each group, to determine if the *HRH2* –1018 G > A polymorphism (rs2067474) is associated with gastric cancer.

ACKNOWLEDGEMENTS

The study was partly supported by the Latvian Government Research Programme BIOMEDICINE 2014–2017 Project Nr. 4 "Study of gastric cancer mortality reduction capability in Latvia".

Sample collection and processing were supported from the resources of the Biobank of Rīga East Clinical University Hospital and Centre of Digestive Diseases "GASTRO".

We acknowledge the Genome Database of Latvian Population, Latvian Biomedical Research and Study Centre for providing data and DNA samples.

We acknowledge the patients who donated their samples for the research, and institution that was involved in sample collection: Rīga East Clinical University Hospital.

We acknowledge aid of Dr. Inta Liepniece-Karele from Rīga East Clinical University Hospital who participated in the histopathological assessment of the biopsy slides.

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Received 4 December 2017
Accepted in the final form 18 August 2018

NAV SAISTĪBAS STARP HISTAMĪNA H2 RECEPTORA GĒNA POLIMORFISMU RS2067474 UN KUŅĢA VĒZI LATVIJAS POPULĀCIJĀ

Histamīnam, mijedarbojoties ar histamīna H2 receptoru (kodē *HRH2* gēns), ir svarīga loma kuņģa gļotādas iekaisuma procesa attīstībā. Polimorfisms rs2067474 – (–1018 G A) *HRH2* gēna promotera pastiprinātājā var būt saistīts ar izmaiņām receptora ekspresijā. Pētījumā mēģināts noskaidrot šī polimorfisma saistību ar kuņģa vēzi un/vai atrofisku gastrītu Latvijas populācijā. Pētījumā iesaistīti: 121 kuņģa vēža pacients un 650 pacienti bez kuņģa vēža, izmeklējot ar augšējo kuņģa zarnu trakta endosksopiju. Genotipēšana rs2067474 veikta ar TaqMan zondēm. A alēles biežums kuņģa vēža pacientiem bija 0,41%, kontroles grupas pacientiem — 1,54% (p = 0,231). Nozīmīgas atšķirības, salīdzinot kuņģa vēža un kontroles pacientu genotipus, netika atrastas (OR = 0,236, CI95% = 0,030–1,896). Atšķirības netika atrastas, salīdzinot pacientu genotipus ar kuņģa gļotādas metaplāziju (n = 165) un bez kuņģa gļotādas metaplāzijas (n = 485) (OR = 0,854, CI95% = 0,288–2,540); un pacientus ar kuņģa gļotādas atrofiju (n = 297) un bez tās (n = 353) (OR = 1,145, CI95% = 0,451–2,906). *HRH2* gēna – 1018 G > A polimorfisms (rs2067474) nav saistīts ne ar kuņģa vēzi, ne ar atrofiska gastrīta pakāpi Latvijas populācijā.